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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,595	05/08/2001	Wei Gu	MNI-080CP	2613

7590 11/29/2002

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EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	12

DATE MAILED: 11/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/851,595	Applicant(s) Wei Gu
	Examiner Prema Mertz	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 11, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 23-32 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 23-32 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group IV (old claims 1-7, 12, drawn to a nucleic acid encoding a protein of SEQ ID NO:11, canceled in favor of new claims 23-32) in Paper No. 11, 10/11/02, is acknowledged. The traversal is on the ground(s) that the restriction is improper and should be withdrawn because there is no undue burden placed upon the Examiner to search Groups II-IV listed in the Restriction Requirement. This argument is found persuasive and Groups II-IV (claims 23-32, drawn to SEQ ID NO:5, 8, 11) will be examined in the instant application.

Specification

2. The use of the trademark ATCC has been noted in this application. It should be capitalized whenever it appears and be accompanied by the ® symbol.

3. There are blank spaces on pages 41-52, 113-114 and on several other pages in the specification, since the ATCC Accession Number has not been recited. Appropriate correction is requested.

4. A new title of the invention is required because the word "novel" is not considered as part of the title of an invention and the Patent and Trademark Office does not include such words at the beginning of the title of the invention. It is suggested that the word "novel" be deleted from the title of the invention. See MPEP. § 606.01.

Claim rejections-35 U.S.C. 101

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. It is clear from the instant specification that the claimed nucleic acid encoding a protein referred to as "large G-protein coupled receptor 6" or "LGR6" (page 3, lines 9-17), is what is termed an "orphan receptor" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins, i.e. the LGR5 mouse protein to which the human LGR6 protein is 65% identical shares similarity to human HG38, rat LGR5 and LGR4 G-protein coupled receptors (see page 114, lines 15-31). The translation product of the LGR6 protein encoded by the claimed nucleic acid, shares sequence homology other putative G-protein coupled receptors (page 114). Until some actual and specific significance can be attributed to the LGR6 protein identified in the specification as having homology to other putative G-protein coupled receptors (page 114), the instant invention is incomplete. However, the instant specification does not disclose any information regarding functional characteristics or the biological activity of the

instant protein encoded by the claimed nucleic acid. While the specification on pages 85-112 describes many activities for the instant protein encoded by the claimed nucleic acid, such as a reagent in screening assays, predictive medicine, and methods of treatment, there is no guidance given about which specific activity/activities the polypeptide encoded by the claimed nucleic acid, would be likely to have. The specification does not demonstrate that the polypeptide actually displays any of these recited activities. In the absence of knowledge of the specific biological significance of the protein encoded by the claimed nucleic acid, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for the nucleic acid encoding the protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

A protein of unknown function would have utility if it can be employed as an indicator of a diseased state or of the presence of a disorder. A disclosed function for the claimed nucleic acid is that it can be used to detect LGR6 mRNA in a biological sample or a genetic alteration in an LGR6 gene and that the LGR6 proteins can be used to treat disorders characterized by insufficient or excessive production of an LGR6 substrate or production of LGR6 inhibitors (see page 86, lines 5-10). However, Applicants have failed to show any differential expression of the instant nucleic acid in normal and diseased tissue. Applicant is only required to identify one substantial credible utility and the employment of this protein only as the subject of further research does not satisfy the utility requirement of 35 U.S.C. § 101 because the courts have interpreted this statute as requiring an invention to have "substantial utility" "where specific benefit exists in currently available form". The

employment of a nucleic acid of the instant invention, as a marker for a disease is not a substantial or specific utility.

Applicants disclose in the specification that the protein encoded by the claimed nucleic acid has homology to G-protein coupled receptors (page 114, lines 15-23). The state of the art is such that functional information can be automatically derived from structural information only to a limited extent, (see Sklonick et al, Nature Biotechnology, Vol.18, No.3, pages 283-287, especially page 286, middle of column 1). Sklonick et al also state that knowledge of the overall structure or domain family is still not enough to confidently assign function to a protein. Therefore, there is little doubt that, after further characterization, the protein is found to be member of the decay accelerating factor family, the claimed protein would have a specific, substantial and credible utility. However, further characterization is part of the invention and until it had been undertaken, the claimed invention is not supported by a specific asserted utility or a well established utility. The claimed invention is directed to a nucleic acid encoding a LGR6 polypeptide of as yet undetermined function or biological significance. Thus, since there is no biological activity disclosed for the protein encoded by the claimed nucleic acid, the claimed invention is not supported by either a specific and substantially asserted utility or a well established utility.

Claims 23-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The instant specification does not disclose a biological activity for the claimed protein,

therefore, there is no specific and substantial asserted utility or well established for the claimed protein. The fact that the claimed nucleic acid encodes a protein that has homology to the rate decay accelerating factor protein is not sufficient to establish a specific and substantially asserted utility or a well established utility for it.

Should Applicants establish an activity for the nucleic acid encoding the LGR6 polypeptide, the instant specification would still fail to adequately describe and enable an isolated a nucleic acid that is least about 90% identical to the nucleotide sequences set forth in claim 23. Applicants do not teach which regions of said polypeptide are critical to encode a functional polypeptide. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a polypeptide having at least about 90% sequence identity, nor does the disclosure provide criteria that explicitly enable such critical features. There is no guidance in the specification as to how one of ordinary skill in the art would generate a polypeptide, other than that exemplified. The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record.

In summary, the amount of experimentation required for one of ordinary skill in the art to use the claimed invention, an isolated polypeptide that is at least 90% identical to the sequences recited in claim 23, would be undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve

the determination of those nucleotide sequences of the disclosed naturally-occurring nucleic acid encoding the LGR6 polypeptide, which are required for functional and structural integrity of the claimed polypeptide. It is this additional characterization of the disclosed polypeptide that is required in order to obtain the functional and structural data needed to permit one to produce a polypeptide which meets both the structural and functional requirements of the instant claim that constitutes undue experimentation.

Claim rejections-35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim 23 is a genus claim. Claim 23 recites "at least about 90% identical" which limitation encompasses nucleic acid variants of the claimed nucleic acids. The term "variants" includes nucleic acid molecules encoding a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to the nucleic acid molecule which encode the amino acid sequence set forth

in SEQ ID NO:5, 8 or 11. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the nucleic acid molecule. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid encoding a protein set forth in SEQ ID NO:5, 8 or 11, alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus of nucleic acid molecules.

6b. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:5, 8, or 11, does not reasonably provide enablement for an isolated nucleic acid molecule comprising a nucleotide sequence

which is at least about 90% identical to the nucleotide sequences as set forth in claim 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Claim 23 is overly broad in its limitation of "at least about 90% identical" because no guidance is provided as to which of the myriad of nucleic acid species encompassed by the claim will retain the desired characteristics. Variants of the nucleic acid encoding the polypeptide can be generated by deletions, insertions, and substitutions of amino acids. However, actual or prophetic examples on expected performance parameters of any of the possible muteins of the protein molecule encoded by the claimed nucleic acid have not been disclosed. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid

shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate a polynucleotide encoding a LGR6 polypeptide other than that exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of claim 23 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

7. Claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is rejected as vague and indefinite in their recitation of the limitation "about 90% identical...". It is unclear whether the "% identity" is "80%, 95% or even 70%".

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
November 14, 2002